PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ET0002PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/13468	International filing date *(day/month/year)* 29.11.2003	Priority date *(day/month/year)* 29.11.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/185		
Applicant LABORATORIOS DEL DR. ESTEVE S.A.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
29.06.2004	09.03.2005
Name and mailing address of the International preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer Cielen, E Telephone No. +31 70 340-4540

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/13468

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-16 as originally filed

Claims, Numbers

1-19 received on 10.01.2005 with letter of 10.01.2005

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☒ the claims, Nos.: 20-25
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/13468

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	-
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	see separate sheet
	No:	Claims	

2. Citations and explanations

see separate sheet

INTERNATIONAL PRELIMINARY EXAMINATION REPORT - SEPARATE SHEET International application No. PCT/EP 03/13468

Re Item I

Basis of the report

The amendments filed with the letter dated 10.01.2005 are in accordance with Article 34(2)(b) PCT.

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

V.i. The claims involve compositions or substances in a method of treatment of the human/animal body. For the assessment of such claims on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

V.ii. Reference is made to the following documents:

D4: WO-A-9737647, cited in the application
D5: Br. J. Pharm., 121, 1997, 711-716 (Ruiz), cited in the application
D11: FR-A-2656525
D12: DE-A-10016356

V.iii. Article 33(2) PCT:

The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-19 is *formally* new in the sense of Article 33(2) PCT.

None of the cited prior art documents discloses the use of a 2,5-

dihydroxybenzenesulfonic compound of general formula I for the treatment and/or prophylaxis of sexual dysfunction in humans, whereby the medicament is administered in a daily dose of ≤ 500mg.

However, attention is drawn to the fact that claims 1-19 relate to a dosage regimen. In the Regional/National phase, such a feature will not be considered to represent a further medical indication from which novelty can be derived on the basis of the principles set out in decision G5/83. In addition, determination of the best individual treatment schedule is typical of the non-commercial and non-industrial medical activities which Article 52(4), EPC intends should remain free from restraint.

At this stage, no in-depth discussion of the arguments brought forward by the Applicant will be held, as they all relate to the Regional/National phase. It is however to be noted that the cited decisions appear to concern *new modes of administration*, which can confer novelty and inventive step to a second medical use claim, contrary to a dosage regimen.

V.iv. Article 33(3) PCT

(a) The problem underlying the present application is the provision of a medicament containing 2,5-dihydroxybenzenesulfonic compounds for the prophylaxis and/or treatment of sexual dysfunction in humans, that avoids the disadvantages (side effects, bad patient compliance) of the medicaments known from the prior art (description, p. 1, par. 4 - p. 2, par. 3). The proposed solution is the use of the same compounds at a total daily dose of less than 500 mg (description, p. 2, par. 4-5; p. 5, par. 5).

(b) The present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-19 does not involve an inventive step in the sense of Article 33(3) PCT.

(1) Document D4 discloses the use of 2,5-dihydroxybenzenesulfonic compounds for the same therapeutic purpose as in the present application at a dosage of 500 mg and higher. This document discloses the use of compounds corresponding to present formula I, in particular calcium dobesilate, ethamsylate and persilate, for normalising the endothelial function and treating sexual dysfunctions, both in patients with vascular disorders of various origins, such as diabetes, as in patients with only a functional problem, and for treating the vascular complications of diabetes and vascular disorders of endothelial origin (p. 1, line 5 - p. 2, line 32; claims). The compounds are administered in a daily dose of about 0.5 to about 2 g, in the form of capsules or tablets (p. 6, lines 14-19). Galenic forms containing 500 mg and

250 mg, respectively, of calcium dobesilate are disclosed (p. 6, line 20 - p. 7, lines 10).

It is respectfully maintained that is not apparent that the selection of a dose of < 500 mg/d (as in the present application; *which could also mean 499 mg*) over a dose of 500 mg/day, as disclosed in the prior art D4, involves an inventive step.

(2) Even as far as the specific dosages in claim 6 (150 to 450 mg and 200 to 400 mg) are concerned, the selection of these dosages does not represent an inventive step in the sense of Article 33(3) PCT, because it is considered a routine practice for the person skilled in the art to try to lower the dosages to overcome the side-effects associated with higher dosages.

In addition, when establishing a dose-response curve for a given pharmaceutical compound, *at least some activity* will be found for the lower dosages. The present application remains silent about the *actual* efficacy of the 2,5-dihydroxybenzenesulfonic compounds at a dosage below 500 mg ("Even at this small dose (< 500 mg) calcium dobesilate results in *enhanced* erectile responses" (p. 16, last line)); finding *some* activity appears therefore not inventive in the light of the prior art document D4.

(3) Moreover, the conclusion of the tests on p. 16, par. 6, is questionable in the light of the prior art. In the present description, the Applicant states that "The concentration of calcium dobesilate [10 µM (see p. 16, par. 2)] used in the *in vitro* experiments described above is in the range of plasma levels achieved after an oral dose of < 500 mg." In D5, it is stated that the same *in vitro* concentrations correspond to an oral dose of 500 mg: "The concentrations of DOBE shown to be effective in the studies [10^{-5}M (see e.g. abstract)] are in the range of the plasma levels found after the common rabbit and human oral dose of 500 mg" (p. 715, left-hand column, par. 1).

In addition, the *in vivo* tests in the present application disclose intravenous administration of calcium dobesilate (10 mg/kg).

It therefore appears questionable that the problem underlying the present application actually has been solved. A positive opinion on inventive step can only be given if and as far as the problem underlying the application actually is solved by all claimed variants (Article 33(3) PCT).

(c) The use of sustained-release formulations having a specific coating or matrix (claims 10-19) is not inventive in the light of the prior art for the following reasons:

(1) The use of orally administered 2,5-dihydroxybenzenesulfonic compounds for the treatment of sexual dysfunction has been previously disclosed (see D4).

(2) The subject-matter of claims 10-19 differs herefrom in that the compounds are

administered in a sustained-release formulation having a specific coating or matrix.

(3) The problem to be solved by the present invention may therefore be regarded as the provision of sustained-release formulations of 2,5-dihydroxybenzenesulfonic compounds having a specific coating or matrix for the treatment of sexual dysfunction.

(4) The solution proposed in claims 10-19 of the present application cannot be considered as involving an inventive step (Articles 33(3) PCT) for the following reasons:

It is generally known that sustained-release formulations can lead to a more equal liberation over time of a medicament, thereby reducing high peak plasma concentrations and thus also side-effects, and that they provide better patient compliance, as repeated administration is avoided. It was therefore obvious for the person skilled in the art to incorporate the 2,5-dihydroxybenzenesulfonic compounds in sustained-release formulations for the treatment of sexual dysfunction.

In addition, from D11 it is known to incorporate ethamsylate in a pulverised form in a sustained release formulation containing a hydroxypropylmethylcellulose and a glycerol ester, such as glycerolmonostearate (p. 2, lines 23-32; p. 4, lines 21-25; Example 3; claims 1, 11).

D12 discloses a slow-release form which can contain ethamsylate or calcium dobesilate in combination with e.g. polymers, such as acrylates, waxes, ethylcellulose, and optionally an outer coating (col. 1, par. [0001]-[0002]; col. 2, par. [0012]; col. 3, par. [0017], [0019]-[0020]; col. 4, par. [0026]-[0027]; col. 7, par. [0063]; col. 8, par. [0087]; col. 9, par. [0095]-[0097], claims 1-4, 8).

The use of the specific matrices and/or coatings was therefore also obvious for the skilled person in view of each of D11 and D12, taken individually.

(d) The dependent claims appear not to contain any features which can account for the presence of an inventive step.

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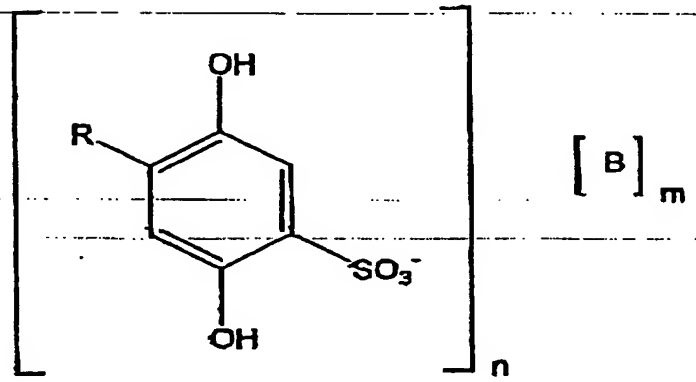
Claims:

1. Use of at least one of the 2,5-dihydroxybenzenesulfonic compounds of general formula I,



I

wherein

R represents H or SO_3^-,

B represents at least one cation

n represents 1 or 2

m represents 1 or 2,

optionally in form of a pharmaceutically acceptable solvate, for the manufacture of a medicament for the prophylaxis and/or treatment of sexual dysfunction in humans, whereby the medicament is administered in a daily dose of the afore mentioned compounds of formula I of < 500 mg.

Clarke, Modet & C°

ESPAÑA

2. Use according to claim 1, characterised in that the cation(s) B is (are) selected from the group consisting of Ca^{2+}, Mg^{2+}, Na^{+}, K^{+} and $[NH_{4-x}R_x]^{+}$, whereby x is 0, 1, 2, 3 or 4 and R represents a branched or unbranched C_{1-4}-alkyl-radical that may be the same or different for x >1.

3. Use according to claims 1 or 2, characterized in that the compound of general formula I is calcium 2,5-dihydroxybenzenesulfonate (calcium dobesilate).

4. Use according to claim 1 or 2, characterized in that the compound of general formula I is diethylamine 2,5-dihydroxybenzenesulfonate (ethamsylate).

5. Use according to claim 1 or 2, characterized in that the compound of general formula I is bis(diethylamine)-2,5-dihydroxybenzene-1,4-disulfonate (persilate).

6. Use according to any one of claims 1-5, characterized in that medicament is administered in a daily dose of compounds of general formula I of 100 to < 500 mg, preferably 150 to 450 mg, particularly preferably 200 to 400 mg.

7. Use according to any one of claims 1-6 for the prophylaxis and/or treatment of erectile dysfunction.

8. Use according to any one of claims 1-7, characterized in that the medicament is suitable for oral administration.

9. Use according to claim 8, characterized in that the medicament is in the form of a tablet, a capsule or a suspension.

10. Use according to claim 8, characterized in that the medicament is in form of multiparticulates, preferably pellets or granules, optionally compressed into a tablet, filled into a capsule or suspended in a suitable liquid.

11. Use according to any one of claims 1-10, characterized in that the medicament comprises at least one of the compounds of general formula I at least partially in a sustained-release form.

12. Use according to claim 11, characterized in that the medicament has at least one coating or matrix comprising at least one sustained-release material.

13. Use according to claim 12, characterized in that the sustained-release material is based on an optionally modified, water-insoluble, natural, semisynthetic or synthetic polymer, or a natural, semisynthetic or synthetic wax or fat or fatty alcohol or fatty acid, or on a mixture of at least two of these afore mentioned components.

14. Use according to claim 13, characterized in that the water-insoluble polymer is based on an acrylic resin, which is preferably selected from the group of poly(meth)acrylates, poly(C_{1-4})dialkylamino(C_{1-4})alkyl (meth)acrylates and/or copolymers thereof or a mixture of at least two of the afore-mentioned polymers.

15. Use according to claim 13, characterized in that the water-insoluble polymers are cellulose derivatives, preferably alkyl cellulose and particularly preferably ethyl cellulose, or cellulose esters.

16. Use according to claim 13, characterized in that the wax is carnauba wax, beeswax, glycerol monostearate, glycerol monobehenate, glycerol ditripalmitostearate, microcrystalline wax or a mixture of at least two of these components.

17. Use according to claims 13 to 16, characterized in that the polymers have been used in combination with one or more plasticizers.

18. Use according to one of claims 8 to 17, characterized in that the medicament comprises an enteric coating.

19. Use according to one of claims 1 to 18, characterized in that the medicament comprises at least one immediate-release coating comprising at least one of the compounds of general formula I.